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Studies on *as*-Triazine Derivatives. XII.[1] Synthesis of Alkenyl-1,2,4-triazine Derivatives

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3-Methyl-5,6-diphenyl-1,2,4-triazine (**1**) was treated with chlorine to give 3-trichloromethyl-5,6-diphenyl-1,2,4-triazine (**2**) as a sole product. On treatment with an excess (4.5 mol eq) of triphenylphosphine, **2** was transformed into α-(5,6-diphenyl-1,2,4-triazin-3-yl)methylenetriphenylphosphorane (**3**) in improved yield. The condensation of **3** with various aldehydes afforded 3-alkenyl-5,6-diphenyl-1,2,4-triazines (**6**).

The application of this method to the 5-position and 6-position of 1,2,4-triazine was also investigated.

Keywords——trichloromethyl-1,2,4-triazine; triphenylphosphine; triazinylmethylenetriphenylphosphorane; aldehyde; alkenyl-1,2,4-triazine; condensation reaction

As reported by Kato *et al.*,[2] 4-trichloromethylpyrimidines reacted with 2 mol eq of triphenylphosphine to give α-chloro-α-(4-pyrimidinyl)methylenetriphenylphosphorane, which underwent condensation with various aldehydes to give the corresponding 4-(α-chloroethenyl)pyrimidines in considerable yields. Later, the reactions were reinvestigated in detail,[3] and the use of excess triphenylphosphine with respect to the 4-trichloromethylpyrimidines was shown to reduce the chlorophosphorane intermediate. In the latter case, the isolated products are 4-alkenylpyrimidines.

In the present paper, we describe the synthesis of alkenyl-1,2,4-triazines (*as*-triazines) from methyl-*as*-triazines as an application of the method described above.

When 3-methyl-5,6-diphenyl-*as*-triazine (**1**)[4] was treated with chlorine in acetic acid in the presence of sodium acetate and acetic anhydride, 3-trichloromethyl-5,6-diphenyl-*as*-triazine (**2**) was obtained as a sole product.[5] On treatment with 2 mol eq of triphenylphosphine in dry benzene under a nitrogen atmosphere, **2** was transformed into α-(5,6-diphenyl-*as*-triazin-3-yl)methylenetriphenylphosphorane (**3**), although the yield of **3** was unsatisfactory. In this case, unlike in the case of 4-trichloromethylpyrimidine, the corresponding chloromethylenephosphorane (**4**) was not isolated. Furthermore, the reaction of triphenylphosphine with 3-dichloromethyl-5,6-diphenyl-*as*-triazine (**5**),[5] prepared by the partial reduction of **2** with tin in concentrated hydrochloric acid, failed to give **3**, and **5** was recovered unchanged from the reaction mixture. Accordingly, compound **4** seems likely to be an intermediate from **2** to **3**.

In connection with the above experiments, the yield of **3** from **2** was shown to be affected by the molar ratio of triphenylphosphine to **2**. As listed in Table I, the use of 4.5 mol eq of triphenylphosphine gave the product in improved yield.

The synthesis of 5,6-diphenyl-*as*-triazine derivatives (**6**) containing an unsaturated side chain at position 3 was readily accomplished by the condensation of **3** with various aldehydes, the results are shown in Table II. Generally, 3-substituted *as*-triazine derivatives are

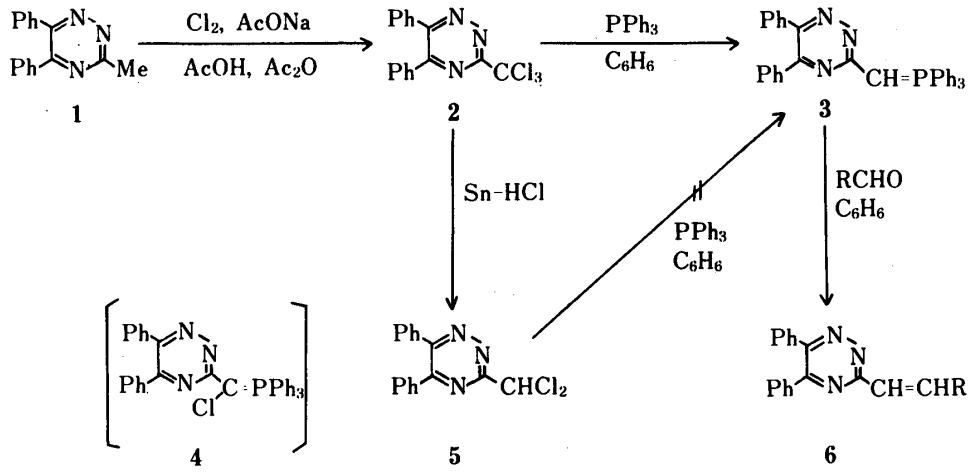


Chart 1

TABLE I. Reaction Conditions for the Preparation of α-(5,6-Diphenyl-*as*-triazin-3-yl)methylenetriphenylphosphorane (3)

Run	Molar ratio		Reaction conditions[a]		Yield of 3 (%)
	as-Triazine (2)	PPh_3	Temp.	Time (h)	
1	1	2	Room temp.	12	46
2	1	2	Reflux	2	30
3	1	3	Room temp.	12	59
4	1	3	Reflux	2	66
5	1	4.5	Room temp.	12	82
6	1	4.5	Room temp.	72	86
7	1	4.5	Reflux	2	79

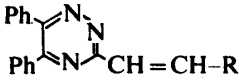
a) The reactions were carried out in dry benzene under nitrogen.

synthesized by the cyclization of 1,2-dicarbonyl compounds with acid amidrazones, but we know of no paper dealing with the preparation of α,β-unsaturated carboxylic amidrazones, so that the synthesis of *as*-triazines containing an alkenyl group at position 3 has not yet been accomplished by direct cyclization.

Then, the application of this method to the 5-position and 6-position of *as*-triazines was investigated. As well as **2**, 5-methyl-3,6-diphenyl-*as*-triazine (**7**) and 6-methyl-3,5-diphenyl-*as*-triazine (**8**) were smoothly chlorinated under the same conditions, and 5-trichloromethyl-3,6-diphenyl-*as*-triazine (**9**) and 6-trichloromethyl-3,5-diphenyl-*as*-triazine (**10**) were obtained in good yields. After **9** and **10** had been converted to **11** and **12**, respectively, by similar procedures, the subsequent condensation of **11** and **12** with various aldehydes also proceeded smoothly, and the alkenyl derivatives (**13**, **14**) were obtained in reasonably satisfactory yields, as listed in Table III.

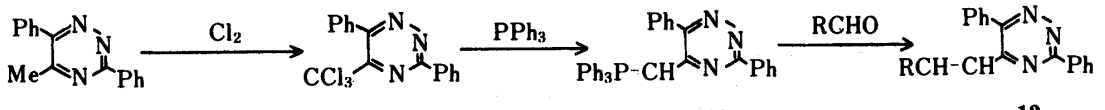
In connection with the synthesis of **7** and **8**, it should be mentioned that the regioselective ring-closure reactions of unsymmetric 1,2-diketone with amidrazones has been reported to be unsuccessful.[6] For example the direct condensation of 1-phenylpropane-1,2-dione (**15**) with benzamidrazone gives rise to mixture of **7** and **8**,[7] although the formation ratio of these triazines is affected by the reaction conditions employed. Thus, in order to obtain **8** selectively, the intramolecular cyclization of the monobenzoylhydrazone (**16**)[8] of **15** was examined by heating with ammonium acetate under various conditions. As shown in Table IV, the reaction of **16** with excess ammonium acetate in ethanol under reflux resulted in the selective formation of **8**.

TABLE II. Preparation of 3-Alkenyl-5,6-diphenyl-*as*-triazines (**6a—f**)

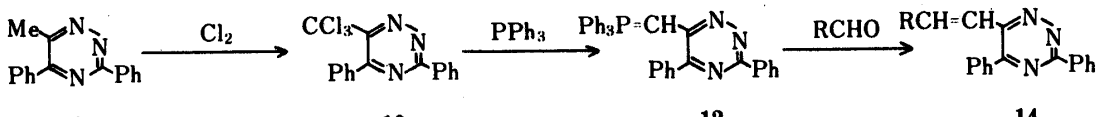


Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (CCl_4) δ (ppm)
6a	Ph	145—146	70	$C_{23}H_{17}N_3$	82.36 (82.35)	5.11 (5.16)	12.53 (12.29)	7.1—7.9 (16H, m), 8.25 (1H, d, J=16 Hz)[b]
6b	Me	82—84	73	$C_{18}H_{15}N_3$	79.09 (78.65)	5.53 (5.42)	15.38 (14.88)	2.15 (3H, d, J=6 Hz), 7.2—7.9 (12H, m)
6c	$Me(CH_2)_2$	75—76	75	$C_{20}H_{19}N_3$	79.70 (79.52)	6.35 (6.38)	13.94 (13.83)	1.05 (3H, t, J=6 Hz), 1.4—1.9 (2H, m), 2.2—2.6 (2H, m), 6.75 (1H, d, J=16 Hz), 7.2—7.6 (11H, m)
6d	$Me(CH_2)_3$	150[a]	37	$C_{21}H_{21}N_3$	79.96 (80.10)	6.71 (6.95)	13.32 (13.17)	0.7—1.2 (3H, m), 1.3—1.8 (4H, m), 6.70 (1H, d, J=16 Hz), 7.0—7.7 (11H, m)
6e	PhCH=CH	142—144	78	$C_{25}H_{19}N_3$	83.07 (83.03)	5.30 (5.26)	11.63 (11.54)	6.7—6.8 (m)[b]
6f	MeCH=CH	146—147	62	$C_{20}H_{17}N_3$	80.24 (80.41)	5.72 (5.82)	14.04 (13.93)	1.90 (3H, d, J=6 Hz), 6.1—6.9 (3H, m), 7.2—8.0 (11H, m)[b]

a) Boiling point (°C) (3 mmHg). *b*) Measured in $CDCl_3$.



7 **9** **11** **13**



8 **10** **12** **14**

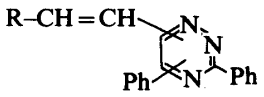
Chart 2

On the other hand, the synthesis of **7** was accomplished by the nucleophilic addition of methylmagnesium iodide to 3,6-diphenyl-*as*-triazine (**19**) followed by the aromatization of the adduct as illustrated in Chart 3.

Namely, the dehydroxy-chlorination of 3,6-diphenyl-5-oxo-2,5-dihydro-*as*-triazine (**17**) with phosphoryl chloride gave 5-chloro-3,6-diphenyl-*as*-triazine (**18**),[9] which was easily hydrogenated to give 3,6-diphenyl-*as*-triazine (**19**). When **19** was allowed to react with methylmagnesium iodide in ether at room temperature, the addition of the Grignard reagent proceeded to give the dihydro-compound (**20**) whose skeleton is supposed to be 2,5-dihydro-*as*-triazine on the basis of its spectral data.[10] When the dihydro-compound (**20**) was treated with potassium permanganate in acetone, **20** underwent aromatization to give **7**, as expected.

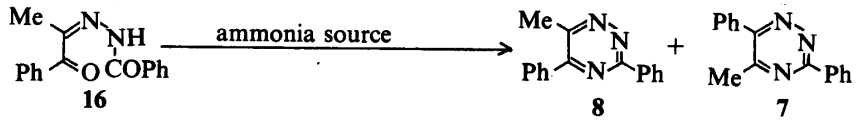
In conclusion, our present investigation appears in principle to provide a synthetic route to *as*-triazine derivatives containing an olefinic side chain at any position, although the availability of some of the starting materials remains a problem.

TABLE III. 5-Alkenyl-(13) and 6-Alkenyl-diphenyl-*as*-triazines (14)



Compd. No.	RCH=CH	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$) δ (ppm)
13a	5-PhCH=CH	177—179	63	$C_{23}H_{17}N_3$	82.36 (82.20)	5.11 (5.12)	12.53 (12.28)	7.1—8.1 (14H, m), 8.40 (1H, d, J=16 Hz), 8.6—9.0 (2H, m)
13b	5-MeCH=CH	123—125	35	$C_{18}H_{15}N_3$	79.09 (79.18)	5.53 (5.62)	15.38 (15.48)	2.05 (3H, d, J=7 Hz), 6.65 (1H, d, J=16 Hz), 7.3—8.0 (9H, m), 8.6—8.8 (2H, m)
14a	6-PhCH=CH	199.5—201	83	$C_{23}H_{17}N_3$	82.36 (82.30)	5.11 (5.03)	12.53 (12.46)	7.1—8.0 (14H, m), 8.15 (1H, d, J=16 Hz), 8.5—8.8 (2H, m)
14b	6-Ph(CH=CH)$_2$	202—203.5	74	$C_{25}H_{19}N_3$	83.07 (82.79)	5.30 (5.41)	11.63 (11.57)	6.7—7.1 (3H, m), 7.2—8.0 (14H, m), 8.5—8.6 (2H, m)
14c	6-MeCH=CH	112—113	62	$C_{18}H_{15}N_3$	79.09 (78.94)	5.53 (5.52)	15.38 (15.21)	1.95 (3H, d, J=7 Hz), 6.65 (1H, d, J=16 Hz), 7.1—8.0 (9H, m), 8.5—8.8 (2H, m)

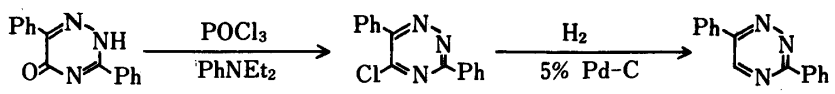
TABLE IV. Reaction Conditions for the Preparation of 6-Methyl-3,5-diphenyl-*as*-triazine (8)



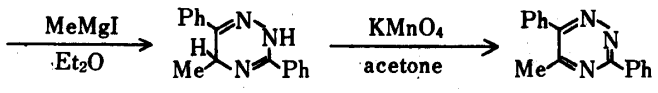
16 **8** **7**

Run	Ammonia source (eq)	Reaction conditions	Ratio of **8** and **7**[a]	Yield of **8** (%)
1	$AcONH_4$ (2)	EtOH, reflux, 12 h	31:1	26
2	$AcONH_4$ (10)	EtOH, reflux, 12 h	9:1	77
3	$AcONH_4$ (20)	EtOH, reflux, 12 h	13:1	64
4	$AcONH_4$ (2)+NH_3	EtOH, 50 °C, 3 h	21:1	62
5	$AcONH_4$ (10)	MeOH, reflux, 12 h	21:1	64

a) The ratio of **8** and **7** was determined by high-performance liquid chromatography [Hitachi 635-TG high-performance liquid chromatograph; column, Hitachi gel #3040; solvent, AcOEt–hexane (30:70, v/v); flow rate, 0.5 ml/min; detector, UV 290 nm] and these ratios were corrected by using the calibration line for authentic samples (**8** and **7**).



17 **18** **19**



20 **8**

Chart 3

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Mass spectra (MS) were taken with Hitachi M-52 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 Mz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

3-Trichloromethyl-5,6-diphenyl-*as*-triazine (2)——3-Methyl-5,6-diphenyl-*as*-triazine (**1**)[4] (4.92 g, 20 mmol) and AcONa (5.3 g, 64 mmol) were dissolved in AcOH (60 ml) and Ac_2O (6 ml). The mixture was heated at 85 °C with vigorous stirring and chlorine gas was blown through the mixture for 3 h. The reaction mixture was made basic with 28% NH_4OH and was extracted with CH_2Cl_2, then dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from Et_2O–hexane to give 5.32 g of **2**, mp 132—133 °C, as yellow prisms. ^{1}H-NMR ($CDCl_3$): 7.3—7.8 (m). *Anal.* Calcd for $C_{16}H_{10}Cl_3N_3$: C, 54.81; H, 2.87; Cl, 30.33; N, 11.98. Found: C, 55.08; H, 2.84; Cl, 30.15; N, 12.06.

α-(5,6-Diphenyl-*as*-triazin-3-yl)methylenetriphenylphosphorane (3)——A solution of PPh_3 (3.5 g, 13.5 mmol) in dry benzene (10 ml) was added dropwise to a solution of **2** (1.05 g, 3 mmol) in dry benzene (50 ml) under nitrogen. The mixture was stirred at room temperature for 72 h under nitrogen, then poured into H_2O. The aqueous layer was separated and the benzene layer was extracted with 1% HCl solution (16 ml) three times. The combined aqueous solution was washed with benzene and made alkaline with K_2CO_3. The separated red oil was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from AcOEt to give 1.3 g (86%) of **3**, mp 214—215 °C (dec.), as red prisms. IR ($CHCl_3$) cm^{-1}: 1500, 1460. ^{1}H-NMR ($CDCl_3$): 8.05—7.10 (m). MS *m/z*: 507 (M^+). *Anal.* Calcd for $C_{34}H_{26}N_3P$: C, 80.45; H, 5.16; N, 8.28. Found: C, 79.93; H, 5.03; N, 8.22.

3-Alkenyl-5,6-diphenyl-*as*-triazines (6a—f)——An aldehyde (2.2 mmol) was dissolved in dry benzene (20 ml) and **3** (1.01 g, 2 mmol) was added thereto. The mixture was heated under reflux for 2.5 h and then concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography, and then recrystallized to give **6a—f**. In the case of **6d**, the reaction was carried out under ice-cooling for 12 h. The analytical data, physical data, and spectral data of **6a—f** are listed in Table I.

5-Trichloromethyl-3,6-diphenyl-*as*-triazine (9)——Following the procedure for the preparation of **2**, treatment of **7** (2.47 g, 10 mmol) and AcONa (2.46 g, 30 mmol) in AcOH (50 ml)–Ac_2O (5 ml) with chlorine gas gave a crude product, which was recrystallized from AcOEt–hexane to give 2.69 g (77%) of **9**, mp 131—132.5 °C, as yellow prisms. ^{1}H-NMR ($CDCl_3$): 7.4—8.0 (m), 8.6—9.0 (m), integral ratio 4 : 1. *Anal.* Calcd for $C_{16}H_{10}Cl_3N_3$: C, 54.81; H, 2.87; Cl, 30.33; N, 11.98. Found: C, 54.65; H, 2.87; Cl, 30.17; N, 11.93.

6-Trichloromethyl-3,5-diphenyl-*as*-triazine (10)——Following the procedure for the preparation of **2**, treatment of **8** (7.41 g, 10 mmol) and AcONa (7.38 g, 90 mmol) in AcOH (150 ml)–Ac_2O (15 ml) with chlorine gas gave a crude product which was recrystallized from AcOEt–hexane to give 6.59 g (63%) of **10**, mp 149.5—151 °C, as yellow prisms. ^{1}H-NMR ($CDCl_3$): 7.2—8.0 (m), 8.4—8.9 (m), integral ratio 4 : 1. *Anal.* Calcd for $C_{16}H_{10}Cl_3N_3$: C, 54.81; H, 2.87; Cl, 30.33; N, 11.98. Found: C, 54.99; H, 2.87; Cl, 29.98; N, 12.01.

α-(3,6-Diphenyl-*as*-triazin-5-yl)methylenetriphenylphosphorane (11)——A solution of PPh_3 (6.65 g, 25 mmol) in dry benzene was added to a solution of **9** (1.76 g, 5 mmol) in dry benzene (100 ml) under nitrogen. The mixture was heated under reflux for 6 h with vigorous stirring. Similar treatment of **3** resulted in the formation of a crude product, which was recrystallized from $CHCl_3$–AcOEt to give 1.44 g (57%) of **11**, mp 245—248 °C, as yellow prisms. ^{1}H-NMR ($CDCl_3$): 7.0—8.0 (m). MS *m/z*: 507 (M^+). *Anal.* Calcd for $C_{34}H_{26}N_3P$: C, 80.46; H, 5.16; N, 8.28. Found: C, 79.91; H, 5.14; N, 8.02.

α-(3,5-Diphenyl-*as*-triazin-6-yl)methylenetriphenylphosphorane (12)——Following the procedure for the preparation of **11**, treatment of **10** (1.76 g, 5 mmol) in dry benzene (100 ml) with PPh_3 (6.55 g, 25 mmol) gave a crude product which was recrystallized from CH_2Cl_2–hexane to give 1.05 g (41%) of **12**, mp 223—228 °C (dec.), as pale red prisms. ^{1}H-NMR ($CDCl_3$): 7.2—8.5 (m). MS *m/z*: 507 (M^+). *Anal.* Calcd for $C_{34}H_{26}N_3P$: C, 80.74; H, 5.16; N, 8.28. Found: C, 80.74; H, 5.13; N, 8.29.

5-Alkenyl-3,6-diphenyl-*as*-triazine (13a, b) and 6-Alkenyl-3,5-diphenyl-*as*-triazine (14a—c)——Following the procedure for the preparation of **6**, treatment of **11** or **12** (2 mmol) with aldehyde (2 mmol) in dry benzene (10 ml) resulted in the formation of a crude product which was recrystallized to give **13** and **14**. The analytical data, physical data and spectral data of **13a, b** and **14a—c** are listed in Table III.

6-Methyl-3,5-diphenyl-*as*-triazine (8)——A mixture of 1-phenylpropane-1,2-dion-2-benzoylhydrazone (**16**)[8] (5.32 g, 0.02 mol) and $AcONH_4$ (15.4 g, 0.2 mol) in absolute EtOH (150 ml) was heated under reflux for 12 h with stirring. The reaction mixture was concentrated under reduced pressure and a small amount of H_2O was added to the residue. The aqueous solution was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with 3 N K_2CO_3 and saturated NaCl solution, then dried over K_2CO_3. After removal of the solvent, the residue was purified by silica gel column chromatography using $CHCl_3$ as an eluent. Recrystallization from AcOEt–hexane gave 3.8 g (77%) of **8**, mp 110—111 °C [lit.[8] mp 109 °C], as yellow prisms. ^{1}H-NMR ($CDCl_3$): 2.83 (3H, s), 7.4—7.9 (8H, m), 8.6—8.8 (2H, m).

3,6-Diphenyl-*as*-triazine (19)——5-Chloro-3,6-diphenyl-*as*-triazine (**18**)[10] (10.7 g, 40 mmol) was dissolved in

benzene (400 ml), and then 5% Pd–C (1.0 g) and Et_3N (8.08 g, 80 mmol) were added. The mixture was shaken under an H_2 stream (1 atm) at room temperature. After absorption of H_2 (1 l, 1 mol eq), the catalyst was filtered off and washed with benzene (50 ml). The filtrate and washing were combined and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane–Et_2O (4:1) as an eluent. Recrystallization from AcOEt gave 7.55 g (81%) of **19**, mp 158—160 °C [lit.[1] mp 159—161 °C], as pale yellow needles.

5-Methyl-3,6-diphenyl-2,5-dihydro-*as*-triazine (20)——A Grignard solution [prepared from 0.73 g (0.01 g atom) of Mg and 4.3 g (30 mmol) of MeI in dry ether (25 ml)] was added dropwise to a solution of 5.83 g (25 mmol) of **19** in dry ether (55 ml) at room temperature under nitrogen and the mixture was vigorously stirred for 30 min. Saturated aqueous NH_4Cl solution was added to the reaction mixture below 0 °C. The separated precipitate was collected by filtration and dissolved in $CHCl_3$ (150 ml) and then the $CHCl_3$ solution was dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from AcOEt to give 5.27 g (85%) of **20**, mp 194—196 °C, as colorless needles. ^{1}H-NMR ($CDCl_3$): 1.36 (3H, d, J=7 Hz), 5.00 (1H, q, J=7 Hz), 7.0—8.2 (11H, m). *Anal.* Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 76.91; H, 6.02; N, 16.76.

5-Methyl-3,6-diphenyl-*as*-triazine (7)——$KMnO_4$ (8.53 g, 54 mmol) was added to a solution of **20** (4.7 g, 19 mmol) in acetone (300 ml) and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was recrystallized to give 4.3 g (92%) of **7**, mp 122—124 °C [lit.[6] mp 123—124 °C], as pale yellow prisms. ^{1}H-NMR ($CDCl_3$): 2.66 (3H, s), 7.3—8.0 (8H, m), 8.4—8.9 (2H, m).

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5) If less than 3 eq of chlorine was used, a considerable amount of **1** remained unchanged, and the product isolated was **2** in unsatisfactory yield.
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7) It is not easy to separate the mixture of 5-methyl-3,6-diphenyl-*as*-triazine (**7**) and 6-methyl-3,5-diphenyl-*as*-triazine (**8**) by silica gel column chromatography.
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